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Brief communication

HPV testing and visual inspection for cervical cancer screening in resource-poor regions

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Human papillomavirus (HPV) infection is accepted as the necessary cause of cervical cancer. HPV testing is highly sensitive for high-grade cervical intraepithelial neoplasia (CIN2–3) and cervical cancer but has modest specificity [1]. Visual inspection with acetic acid (VIA) is another possible alternative to cytology for low-resource regions because it is inexpensive, requires minimum training, and provides rapid results; however, VIA alone is not sufficiently accurate [2].

We propose a strategy of HPV testing and immediate VIA among HPV-positive women. HPV testing would provide sensitivity, while VIA would triage to treatment only the most severe lesions. This screening strategy would target 25–49-year-old women considering HPV natural history (frequent infections in young women are usually benign), VIA performance (declines with age), and age-specific rates of cervical cancer (rare under 25).

We evaluated 5564 patients, 25–49 years old, enrolled in a population-based study of HPV and cervical neoplasia in Costa Rica [3]. Women were followed-up for 7 years. They were referred to colposcopy for any cytologic abnormalities (conventional Pap or ThinPrep), positive Cervigram, or clinical suspicion of cancer detected during standardized screening examinations performed periodically throughout follow-up. At exit, women with persistent HPV infection were also referred.

We estimated the performance of a single screening at cohort enrollment using baseline HPV testing and VIA. We simulated VIA by evaluating Cervigrams (NTL Worldwide, Fenton, MO) among women with 13 oncogenic HPV infections [4]. This analysis was conducted in anticipation of a low-cost, same-day HPV test.

We reasoned that VIA criteria optimal for use following HPV testing should be more sensitive than current criteria in the general population, because the pool of women would be much smaller (HPV-positives) with higher probability of disease. We based triage on the simple distinction between negative vs. positive for any degree of acetowhite epithelium (Fig. 1), which also make VIA simpler and possibly more reproducible.

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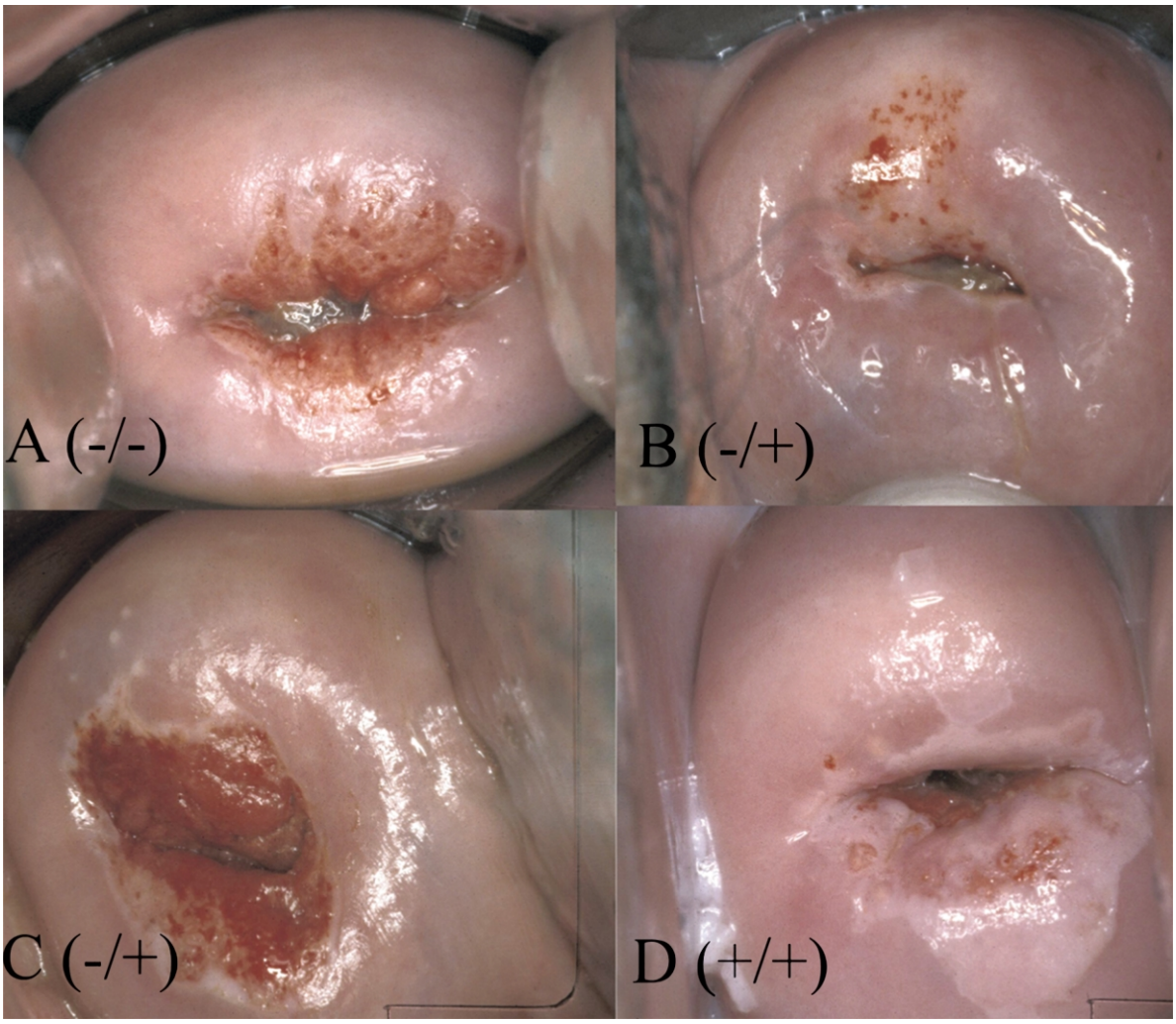

Fig. 1. Examples of Cervigrams used to simulate added visual inspection (VIA). The proposed VIA criteria would classify women as either strictly negative or positive for *any* degree of acetowhitening, instead of the current criteria that consider as positive only more definite lesions. Shown are examples of Cervigrams that were negative by both the old and new VIA criteria (a); negative by the old criteria but positive by the new one (b and c); and positive by both the old and new VIA criteria (d). Cases b, c, and d had histologic diagnoses of CIN2 or 3.

We calculated for HPV testing, HPV testing combined with VIA, and optimized conventional cytology (ASCUS or greater), the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence intervals. Differences between clinical parameters were tested for statistical significance (two-sided) by McNemar statistics.

We defined as cases those women with CIN2–3 diagnosed at or within two years after enrollment or cancer diagnosed at or within 7 years after enrollment ($n=116$; 12 cancers). We adopted this strategy to account for missed prevalent disease and associated verification bias inherent in a cross-sectional assessment. HPV-DNA positivity followed by VIA yielded sensitivity of 65.5% (Table

Table 1
A comparison of the clinical performance of HPV testing (I), HPV testing combined with visual inspection (II), and any cytologic abnormalities (atypical squamous cells [ASC] or more severe) (III) for detection of enrolment ≥CIN2 cases, CIN2 or CIN3 diagnosed within 2 years, or cancer diagnosed within 7 years after enrollment for women aged 25–49 years[a]

	Total	% Treated (cancer)	≥CIN2 (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV
Women, aged 25–49 years	5564		116 (12)				
I. Oncogenic HPV DNA positive	595	10.7% (9.9–11.5%)	94 (10)	81.0% (72.7–87.7%)	90.8% (90.0–91.6%)	15.8% (13.0–19.0%)	99.56% (99.33–99.72%)
II. Oncogenic HPV DNA and visual positive I. vs. II.	243	4.4% (3.8–4.9%) **$P<0.0001$**	76 (7)	65.5% (56.1–74.1%) **$P<0.0001$**	96.9% (96.4–97.4%) **$P<0.0001$**	31.3% (25.5–37.5%) **$P<0.0001$**	99.25% (98.98–99.46%) **$P<0.0001$**
III. Conventional PAP (≥ASC) II. vs. III.	392	7.0% (6.4–7.7%) **$P<0.0001$**	71 (8)	61.2% (51.7–70.1%) $P<0.075$	94.1% (93.5–94.7%) **$P<0.0001$**	18.1% (14.4–22.3) **$P<0.0001$**	99.13% (98.84–99.36%) $P=0.60$

[a] Differences in the clinical parameters between HPV testing and HPV testing combined with visual inspection (I. vs. II.) and between HPV testing combined with visual inspection and conventional Pap cytology (II. vs. III.) were tested for statistical significance (two-sided) (bold indicates $P<0.05$) by calculating paired statistics.

1), comparable with the Pap smear interpreted by a Costa Rican expert ($P=0.75$), but substantially increased specificity to 96.9% ($P<0.0001$) and PPV to 31.3% ($P<0.0001$). As a point of reference, HPV testing alone had a higher sensitivity, lower specificity, lower PPV, and higher NPV of 81.0%, 90.8%, 15.8%, and 99.6%, respectively.

We conclude that adding VIA for triage of oncogenic HPV positive women may be viable for screening, with performance possibly better than optimized Pap smear in resource-poor regions, provided that a low cost, same-day HPV test can be developed. This strategy would be best suited to regions in which screening would only take place once or twice in a woman's life, and would permit a same-day, 'see and treat' program that would minimize over-treatment. Specifically, the treated women in this protocol would all be infected with oncogenic HPV which confer substantially elevated long-term risk of high-grade CIN and cancer.

We propose this dual strategy in the hope of formal cost-utility investigations and as further motivation for the development of: (1) inexpensive, robust HPV tests; and (2) complementary VIA criteria.

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